AMENDMENT TO THE CLAIMS

- **Format of Claim Amendments**

Applicant has amended the claims as indicated below. Pursuant to the revised format to 37 C.F.R. 1.121 adopted by the USPTO in July of 2003, Applicant herein submits only one version of the claims with markings to show changes. A detailed listing of all claims that are, or were in the application, are presented.

COMPLETE LIST OF CLAIMS THAT ARE OR HAVE BEEN BEFORE THE OFFICE AFTER ENTRANCE OF THE AMENDMENTS MADE HEREIN (next Page)

1. (CURRENTLY AMENDED) A method of screening for inhibitors of beta-amyloid production comprising,

1) contacting a potential inhibitor of beta-amyloid production and a tagged inhibitor of beta-amyloid production with at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide, wherein the macromolecule is a secretase selected from ~~alpha~~ α-secretase, β ~~beta~~-secretase, and ~~gamma~~ γ-secretase, said macromolecule containing a binding site specific for said tagged inhibitor of beta-amyloid production;
2) separating the tagged inhibitor of beta-amyloid production bound to said macromolecule from the tagged inhibitor of beta-amyloid production free from said macromolecule; and
3) determining an inhibitory concentration of the potential inhibitor of beta-amyloid production from the concentration of tagged inhibitor of beta-amyloid production bound to said macromolecule.

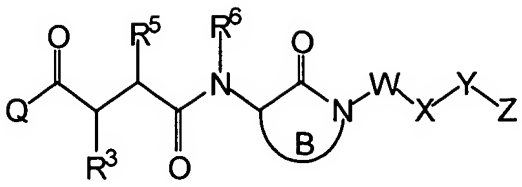
2. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluoroscence labeled inhibitor of beta-amyloid production or a biotin labeled inhibitor of beta-amyloid production.

3. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

4. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium or iodine radiolabeled inhibitor of beta-amyloid production.

5. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium radiolabeled inhibitor of beta-amyloid production.

6. (CURRENTLY AMENDED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I):



(I)

wherein:

at least one atom of the compound of the Formula (I) is radiolabeled;

Q is NH_2;

R^3 is C_1-C_6 alkyl substituted with 0-1 R^4;

R^4 is H, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} carbocycle, C_6-C_{10} aryl, or 5 to 10 membered heterocycle;

R^5 is H, OR^{14};

C_1-C_6 alkyl substituted with 0-3 R^{5b};

C_1-C_6 alkoxy substituted with 0-3 R^{5b};

C_2-C_6 alkenyl substituted with 0-3 R^{5b};

C_2-C_6 alkynyl substituted with 0-3 R^{5b};

C_3-C_{10} carbocycle substituted with 0-3 R^{5c};

C_6-C_{10} aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5b}, at each occurrence, is independently selected from:

H, C_1-C_6 alkyl, CF_3, OR^{14}, Cl, F, Br, I, =O, CN, NO_2, $NR^{15}R^{16}$;

C_3-C_{10} carbocycle substituted with 0-3 R^{5c};

C_6-C_{10} aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5c}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2, $NR^{15}R^{16}$, or CF_3;

R^6 is H;

C_1-C_6 alkyl substituted with 0-3 R^{6a};

C_3-C_{10} carbocycle substituted with 0-3 R^{6b}; or

C_6-C_{10} aryl substituted with 0-3R^{6b};

R^{6a}, at each occurrence, is independently selected from H, C_1-C_6 alkyl, OR^{14}, Cl, F, Br, I, =O, CN, NO_2, $NR^{15}R^{16}$, phenyl or CF_3;

R^{6b}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2, $NR^{15}R^{16}$, or CF_3;

W is $-(CR^8R^{8a})_p-$;

p is 0 to 4;

R^8 and R^{8a}, at each occurrence, are independently selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl and C_3-C_8 cycloalkyl;

X is a bond;

C_6-C_{10} aryl substituted with 0-3 R^{Xb};

C_3-C_{10} carbocycle substituted with 0-3 R^{Xb}; or

5 to 10 membered heterocycle substituted with 0-3 R^{Xb};

R^{Xb}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2, $NR^{15}R^{16}$, or CF_3;

Y is a bond or $-(CR^9R^{9a})_t$-V-$(CR^9R^{9a})_u-$;

t is 0 to 3;

u is 0 to 3;

R^9 and R^{9a}, at each occurrence, are independently selected from H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

V is a bond, -C(=O)-, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^{19})-$, $-C(=O)NR^{19b}-$, $-NR^{19b}C(=O)-$, $-NR^{19b}S(=O)_2-$, $-S(=O)_2NR^{19b}-$, $-NR^{19b}S(=O)-$, $-S(=O)NR^{19b}-$, -C(=O)O-, or -OC(=O)-;

Z is H;

C_1-C_8 alkyl substituted with 0-2 R^{12};

C_2-C_4 alkenyl substituted with 0-2 R^{12};

C_2-C_4 alkynyl substituted with 0-2 R^{12};

C_6-C_{10} aryl substituted with 0-4 R^{12b};

C_3-C_{10} carbocycle substituted with 0-4 R^{12b}; or

5 to 10 membered heterocycle substituted with 0-3 R^{12b};

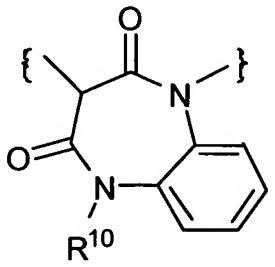
R^{12} is aryl substituted with 0-4 R^{12b};

C_3-C_{10} carbocycle substituted with 0-4 R^{12b}; or

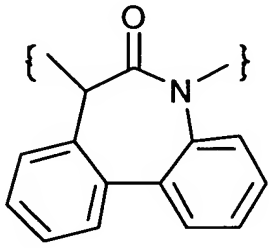
5 to 10 membered heterocycle substituted with 0-3 R^{12b};

R^{12b}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2, $NR^{15}R^{16}$, or CF_3;

B is



or



R^{10} is H, $C(=O)R^{17}$, $C(=O)OR^{17}$, $C(=O)NR^{18}R^{19}$,

$S(=O)_2NR^{18}R^{19}$, $S(=O)_2R^{17}$;

C_1-C_6 alkyl optionally substituted with R^{10a};

C_6-C_{10} aryl substituted with 0-4 R^{10b};

C_3-C_{10} carbocycle substituted with 0-3 R^{10b}; or

5 to 10 membered heterocycle optionally substituted with 0-3 R^{10b};

R^{10a}, at each occurrence, is independently selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OR^{14}, Cl, F, Br, I, =O, CN, NO_2, $NR^{15}R^{16}$, phenyl or CF_3;

R^{10b}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2, $NR^{15}R^{16}$, or CF_3;

R^{14} is H, phenyl, benzyl, C_1-C_6 alkyl, or C_2-C_6 alkoxyalkyl;

R^{15}, at each occurrence, is independently selected from H, C_1-C_6 alkyl, benzyl, phenethyl, -C(=O)-(C_1-C_6 alkyl) and -S(=O)$_2$-(C_1-C_6 alkyl);

R^{16}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, benzyl, phenethyl, -C(=O)-(C_1-C_6 alkyl) and -S(=O)$_2$-(C_1-C_6 alkyl);

R^{17} is H, phenyl, benzyl, C_1-C_6 alkyl, or C_2-C_6 alkoxyalkyl;

R^{18}, at each occurrence, is independently selected from H, C_1-C_6 alkyl, benzyl, phenethyl, -C(=O)-(C_1-C_6 alkyl) and -S(=O)$_2$-(C_1-C_6 alkyl); and

R^{19}, at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, phenyl, benzyl, phenethyl, -C(=O)-(C_1-C_6 alkyl) and -S(=O)$_2$-(C_1-C_6 alkyl); and

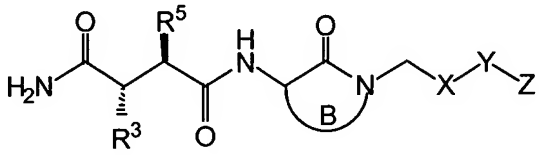
R^{19b} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or phenethyl~~; and~~

~~R^{20} is H or C_1-C_6 alkyl~~.

7. (ORIGINAL) The method of Claim 6 wherein R^3 is C_3-C_6 alkyl.

8. (ORIGINAL) The method of Claim 6 wherein R^3 is C_3-C_6 alkyl substituted with about 1 to about 4 ^3H.

9. (ORIGINAL) The method of Claim 6 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (II):



(II)

wherein:

at least one atom of the compound of the Formula (II) is radiolabeled.

10. (ORIGINAL) The method of Claim 9 wherein R^3 is C_3-C_6 alkyl substituted with about 1 to about 4 ^3H.

11. - 12 (CANCELLED)

13. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide comprises α ~~alpha-~~, β ~~beta-~~ or ~~gamma~~ γ-secretase.

14. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and/or the production of beta-amyloid peptide comprises:

(1) β secretase;

(2) α secretase; or

(3) γ secretase;

~~or any fragment or derivative thereof;~~ said macromolecule containing a binding site specific for said tagged inhibitor of beta-amyloid production.

15. (ORIGINAL) The method of Claim 1 wherein the inhibitory concentration is half maximal inhibitory concentration.

16. (PREVIOUSLY PRESENTED)A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

17. (CURRENTLY AMENDED) A method for treating ~~degenerative neurological disorders involving similar to~~ Alzheimer's Disease, ~~accumulative beta-amyloid production~~ comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

18. (PREVIOUSLY PRESENTED) A method for treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt form thereof.

19. (CANCELLED)

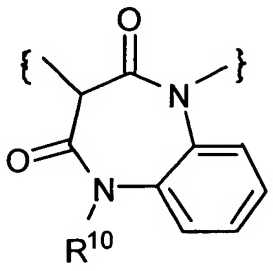
20. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluoroscence labeled inhibitor of beta-amyloid production, or a biotin labeled inhibitor of beta-amyloid production.

21. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

22. (PREVIOUSLY PRESENTED) The method of Claim 1 wherein the tagged inhibitor is radiolabeled with one or more radioisotope selected from ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{123}I, ^{125}I, and ^{131}I.

23.-35. (CANCELLED)

36. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula as claimed in claim 1 wherein ring B is



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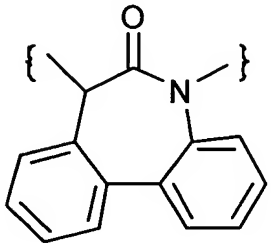


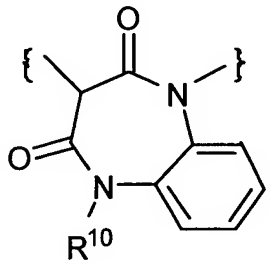
37. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is α ~~alpha~~-secretase, β ~~beta~~-secretase, or γ -secretase, ~~or a fragment thereof~~ containing a binding site specific for said tagged inhibitor of beta-amyloid production.

38. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is γ ~~gamma~~-secretase ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

39. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

40. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on γ gamma-secretase ~~or a fragment of gamma-secretase~~; wherein the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

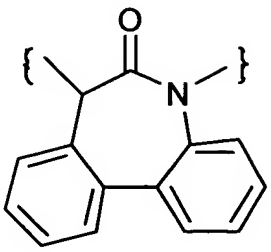
41. (PREVIOUSLY PRESENTED) An inhibitor of beta-amyloid production of Claim 6 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein B is



;

and the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

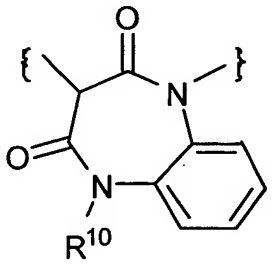
42. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 6 comprising a compound which interacts with a binding site on ~~gamma~~ γ-secretase ~~or a fragment of gamma-secretase~~; wherein said binding site is a specific binding site for a compound of Formula (I) wherein B is



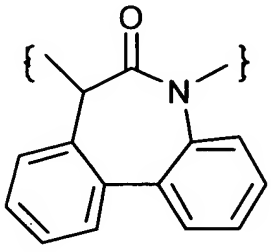
;

and the compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

43. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 6 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is:



or



44. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is α ~~alpha-~~,

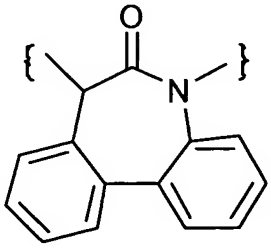
β ~~beta-~~, or ~~gamma~~ γ-secretase ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

45. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is ~~gamma-~~ secretase or a fragment thereof, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

46. (PREVIOUSLY PRESENTED)A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

47. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on α ~~alpha-~~, β ~~beta-~~, or ~~gamma~~ γ-secretase ~~or a fragment thereof~~; wherein said tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

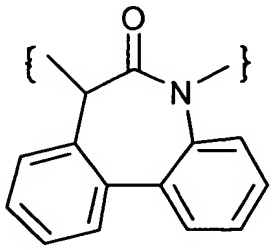
48. (PREVIOUSLY PRESENTED)A tagged inhibitor of beta-amyloid production of Claim 6 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is



;

and the tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

49. (PREVIOUSLY PRESENTED) A tagged inhibitor of beta-amyloid production of Claim 48 comprising a tagged compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I) wherein ring B is:

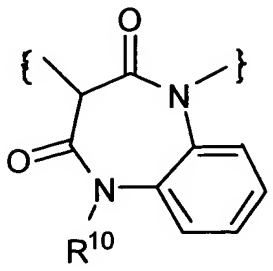


;

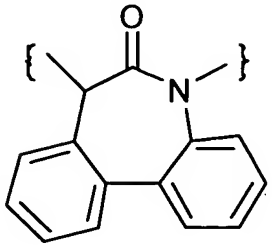
and the tagged compound demonstrates a half maximal inhibitory concentration of less than 10 micromolar for beta-amyloid production.

50. – 53. (CANCELLED)

54. (PREVIOUSLY PRESENTED) A method of treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production, or a pharmaceutically acceptable salt form thereof, wherein said inhibitor of beta-amyloid production binds to a binding site on a macromolecule involved in the production of beta-amyloid peptide and effects a decrease in production of beta-amyloid peptide;
wherein said binding site is a specific binding site for a compound of Formula (I) of Claim 6 wherein ring B is:

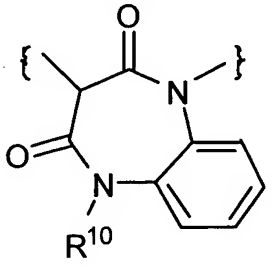


or



55. (CURRENTLY AMENDED) The method of Claim 54 wherein the macromolecule comprises α - secretase, β - secretase, or γ -secretase, ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

56. (PREVIOUSLY PRESENTED) A method of Claim 54 wherein the binding site is a specific binding site for a compound of Formula (I) wherein ring B is:



57. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises α secretase, β secretase, or γ secretase, ~~or a fragment~~ ~~thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

58. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises γ -secretase, ~~or a fragment thereof~~, containing a binding site specific for said tagged inhibitor of beta-amyloid production.

59. (PREVIOUSLY PRESENTED) A method of *in vivo* diagnostic imaging comprising administering to a subject a diagnostically effective amount of a radiolabeled inhibitor of Claim 6 of beta-amyloid production.

60. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

61. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of Alzheimer's disease.

62. (ORIGINAL) A method of Claim 59 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

63. (PREVIOUSLY PRESENTED) A method of Claim 59 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{123}I, ^{125}I, and ^{131}I.

64. (CURRENTLY AMENDED) [[A]] The method of Claim 59 wherein the tagged inhibitor of beta-amyloid production is a compound selected from the group ~~any compound~~ found ~~capable of~~ binding a γ ~~gamma~~-secretase ~~or fragment thereof containing~~ at a binding site specific for said tagged inhibitor of beta-amyloid production, ~~such as~~ consisting of 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives, N-aryl amino acid esters, N-heteroaryl amino acid esters, N-arylacetyl amino acid amides, N-heteroarylacetyl amino acid amides, and N-alkylacetyl amino acid amides, N-arylacetyl amino acid esters, N-heteroarylacetyl amino acid esters, and N-alkylacetyl amino acid esters, N-aryl amino acid derivatives, N-heteroaryl amino acid derivatives, and cycloalkyl, lactam, lactone and related compounds.

65. (PREVIOUSLY PRESENTED) A method of Claim 59 wherein the inhibitor of β amyloid production exhibits activity as an inhibitor of γ secretase.

66. - 69. (CANCELLED)

70. (CURRENTLY AMENDED) A method of Claim 59 wherein the inhibitor of beta-amyloid production is selected from:

(1) an inhibitor of β secretase;

(2) an inhibitor of α secretase; ~~or~~

and

(3) an inhibitor of γ secretase.

71. (PREVIOUSLY PRESENTED) A pharmaceutical composition comprising a compound of Claim 6 suitable for in vivo diagnostic imaging comprising a radiolabeled inhibitor of beta-amyloid production.

72. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

73. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of Alzheimer's disease.

74. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

75. (PREVIOUSLY PRESENTED) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{123}I, ^{125}I, and ^{131}I.

76. (CURRENTLY AMENDED) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is a compound selected from the group ~~any compound~~ found ~~capable of~~ binding a γ secretase, ~~or fragment thereof containing~~ at a binding site specific for said tagged inhibitor of beta-amyloid production, ~~such as~~ consisting of 5-amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives, N-aryl amino acid esters, N-heteroaryl amino acid esters, N-arylacetyl amino acid amides, N-heteroarylacetyl amino acid amides, and N-alkylacetyl amino acid amides, N-arylacetyl amino acid esters, N-heteroarylacetyl amino acid esters, and N-alkylacetyl amino acid esters, N-aryl amino acid derivatives, N-heteroaryl amino acid derivatives, and cycloalkyl, lactam, lactone and related compounds.

77. (PREVIOUSLY PRESENTED) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is an inhibitor of γ-secretase.